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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/286,874	04/06/1999	FRANK L. GRAHAM	ADVEC9	5534

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VAN DYKE & ASSOCIATES, P.A.
7200 LAKE ELLENOR DRIVE, SUITE 252
ORLANDO, FL 32809

EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/05/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/286,874	Graham et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 18, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above, claim(s) *5-7 and 10-12* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 8, 9, and 13-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed April 6, 1999, is a continuation in part of 09/251,955, filed February 17, 1999, abandoned, which is a continuation in part of application 08/473,168, filed June 7, 1995, now US Patent 5,919,676, which is a continuation in part of application 08/250,885, filed May 31, 1994, now US Patent 6,140,087, which is a continuation in part of application 08/080,569, filed June 24, 1993, abandoned.

This application is also a continuation in part of 08/719,217, filed September 25, 1996, now US Patent 6,080,569, which is a continuation in part of 08/473,168, filed June 7, 1995, now US Patent 5,919,676, which is a continuation in par of application 08/250,885, filed May 31, 1994, now US Patent 6,140,087, which is a continuation in part of application 08/080,727, filed June 24, 1993, abandoned.

Applicants amendment filed February 18, 2003, paper number 18, has been received and entered. The specification has been amended. Claims 1-15 are pending.

Election/Restriction

Claims 5-7 and 10-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7. Claims 1-4, 8, 9 and 13-15 are currently under examination.

This application contains claims drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

The amended claim for priority is not consistent with that provided on the bibliographic sheet. The bibliographic sheet should be updated to indicate the additional applications to which priority is claimed and the correct relationship and status of other applications previously listed.

Appropriate correction is required.

Applicant's claim for domestic priority under 35 U.S.C. 120 and/or 121 is acknowledged. However, the applications upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for the claimed invention of this application. Specifically, upon review of the abandoned applications and issued US patents support for the instant invention as it is drawn to a adenoviral vector system wherein different serotype are used to package the adenoviral vector is

first found in the present application. Further, while support for adenoviral vectors using the Cre/lox system has literal support in previous applications, the specific combination of the Cre/lox and serotype changing first appears in the instant application. Accordingly, the priority date given the pending claims is the filing date of this application, April 6, 1999.

Oath/Declaration

The substitute declaration filed February 18, attached to paper number 18, is in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8, 9 and 13-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yang *et al.* (J Viriol. 69:2004-2015), Mack *et al.* (Hum. Gene Ther., 8:99-109), Kass-Eisler *et al.* (Gene Ther., 3(2):154-162) and Graham *et al.* (WO 98/13510).

Applicants note that the specification has been amended to include a claim of priority to application 08/719,217 from which the Graham *et al.* reference WO 98/13510 arose. Accordingly, it is argued that the Graham et al. publication no longer can be used as a reference. Additionally, it is noted that the inventors among the priority documents, in particular 08/719,217, are different. Applicants note that the two applications have two common inventors, and the inventor not listed in the present application is not an inventor of the present invention. It is noted that if further clarification is required a declaration would be provided. See Applicants amendment, page 3. Applicants' comments and arguments have been fully considered.

As noted above, the claim for priority given the instant invention is the filing date of the instant application, April 6, 1999. The publication date of WO 98/13510 is April 2, 1998, thus it is a 102(b) type reference. The amendment to the specification has not obviated the use of the Graham et al. reference, therefore, the rejection is maintained.

Additionally, it is noted that the Graham *et al.* reference is relied upon for the teaching of an adenoviral vector which contains the lox sequences which first appears in dependent claim 3. With respect to the broader independent claims and broader dependent claims not specifically reciting the use of the Cre recombinase, it is noted that the combination of Yang *et al.*, Mack *et al.*, and Kass-Eisler *et al.* make obvious altering the serotype of an adenoviral vector

encompassed by these broader claims. As set forth in the previous office action, Yang *et al.* teach that while recombinant adenoviruses have been efficiently used to reconstitute CFTR expression in the lungs of CF patients (page 2004, middle of first column), a fundamental problem for the continued use of such vectors has been the subjects immunological response to the vectors. More specifically, Yang *et al.* teach improvements in vector design to prevent destructive CTL may prolong the effectiveness of single gene therapy treatment, however multiple treatments will be required in a therapeutic protocol (page 2014, middle of first column), and conclude that improvements in minimizing endogenous viral protein expression alone will not address the problem of re-administration (page 2014, second column). Both Mack *et al.* and Kass-Eisler *et al.* teach one means to use adenoviral vectors and to circumvent anti-adenoviral neutralizing immunity is to sequentially re-administering adenoviral vectors packaged with alternate serotype of the same or different adenoviral subgroups of different serotype. Kass-Eisler *et al.* specifically teaches that "if a battery of 6-12 different adenovirus vectors were generated based on different serotype backbones...it may be possible to administer a therapeutic gene a minimum of 6-12 times" (page 160, second column). Given the limitations of multiple administrations and use of a single vector as taught by Yang *et al.*, one would have been motivated to modify the adenoviral vector as taught by Mack *et al.* and Kass-Eisler *et al.* for more effective re-administration of the vector. The level of skill in the art is high, and there would have been a reasonable expectation of success given the ability of the artisan to

manipulate an adenoviral vector as exemplified in the various materials and methods sections of the cited references.

With respect to the teaching of WO 98/13510, Graham *et al.* discloses an adenovirus vector delivery system comprising a helper dependent adenovirus vector, hdAd (Ad5-based). The vectors taught comprise a genome substantially devoid of adenoviral protein coding sequences (*i.e.* gutless vectors), but containing the 5' and 3' LTRs, and polynucleotide sequences encoding a gene of interest operatively linked to expression control sequences. The system also includes the teaching for an Ad5 helper adenovirus of the same serotype encoding all functions required to facilitate hdAd genome packaging and replication, wherein the helper adenoviruses themselves do not package into infectious virus particles due to cre recombinase-mediated deletion. Further, the adenoviral vectors taught contain lox sites, and when used in conjunction with the addition of Cre recombinase can be used for the insertion and/or deletion of sequences from the adenoviral vectors. In particular, it is taught the lox sites can be inserted on either side of the psi packaging sequence for the subsequent removal of the sequence (see summary of final vector set forth in figure 1). Further, the vectors taught by Graham *et al.* are capable of incorporating large polynucleotide sequences, such as exemplified by CFTR gene taught in Yang *et al.* However, Graham *et al.* does not teach or suggest the use of multiple helper adenoviruses of different serotype relative to the helper dependent vector for the purpose of creating different and distinct genetically identical adenoviral vectors wherein each member of the series has a different serotype conferred by the helper or wherein the members of the series do not produce

cross-reactive antibodies. The gutless adenoviral vector taught by Graham *et al.* provides an improved vector which addresses the art recognized problem of viral protein expression for one administration, however the use of the this vector will be limited to single administration gene therapy protocols. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the protocols taught by Mack *et al.* and Kass-Eisler *et al.* to alter the serotype of the adenoviral vector taught by Graham *et al.* One having ordinary skill in the art would have been motivated to use the gutless adenoviral vector taught by Graham *et al.* in the protocols of Yang *et al.* because of its ability to incorporate the large polynucleotide sequences such as the CFTR gene. Again, the level of skill in the art is high, and there would have been a reasonable expectation of success given the ability of the artisan to manipulate the adenoviral vector as exemplified in the various materials and methods sections and in the working examples of Graham *et al.*, to provide multiple host cells for packaging a given vector as set forth in Mack *et al.* and Kass-Eisler *et al.*

Thus, the claimed invention as a whole was clearly *prima facie* obvious, and the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Deborah Crouch

Joseph T. Woitach

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630